



Egyptian Society for Joint Diseases and Arthritis
The Egyptian Rheumatologist

www.rheumatology.eg.net
www.sciencedirect.com



ORIGINAL ARTICLE

Prevalence of peripheral neuropathy in Egyptian hepatitis C virus patients: Correlation to some clinical and laboratory parameters

Manal Aly Abdel Khalek ^a, Amal Mohamad El-barbary ^{a,*}, Ferial Salah Elkalla ^b,
Salwa Abdel-Moneim Essa ^c

^a Rheumatology and Rehabilitation Department, Faculty of Medicine, Tanta University, Egypt

^b Tropical Medicine Department, Faculty of Medicine, Tanta University, Egypt

^c Clinical Pathology Department, Faculty of Medicine, Tanta University, Egypt

Received 24 January 2012; accepted 2 April 2012

Available online 19 May 2012

KEYWORDS

Hepatitis C virus;
Peripheral neuropathy;
Anti-neuronal antibody;
Cryoglobulins

Abstract *Aim of the work:* The present study was undertaken to assess prevalence and characteristics of peripheral neuropathy (PN) in Egyptian hepatitis C virus (HCV) patients.

Patients and methods: Eighty newly diagnosed HCV patients were enrolled, with 20 healthy volunteers. All were subjected to: full clinical examination, neurological examination, laboratory assessment including: routine blood tests, ESR, CRP, RF, ANA, C4, cryoglobulins (CGs), anti-GM1 antibodies, HCV antibodies, Quantitative PCR, abdominal ultrasonography, liver biopsy, and electrophysiological assessment.

Results: Thirty-six patients (45%) had clinical neuropathy, 18 patients (22.5%) had subclinical neuropathy. Thirty-eight out of the 54 PN patients (70.3%) showed axonal neuropathy which is mainly sensory affecting lower limbs. Twelve patients showed +ve cryoglobulinemia, all of them had neuropathy (10 clinical, 2 subclinical). Abnormal titers of anti-neuronal antibodies were associ-

* Corresponding author. Address: Faculty of Medicine, Elgesheh Street, Tanta, Gharbia, Egypt. Tel.: +20 0101264626.

E-mail address: ml_barbary@yahoo.com (A.M. El-barbary).

Peer review under responsibility of Egyptian Society for Joint Diseases and Arthritis.



Production and hosting by Elsevier

ated with electrophysiological abnormalities in 50 out of the 54 PN patients. PN correlated with age, disease duration, ESR, CRP, RF, HCV viraemia, CGs, anti-GM1 and hypocomplementinemia.

Conclusions: PN exists in high prevalence among Egyptian HCV patients, and is associated with CG. It is mainly of axonal sensory type more affecting lower limbs. HCV patients should be investigated for the presence of CGs even in the absence of clinical manifestations.

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1. Introduction

Hepatitis C virus (HCV) is a parenterally transmitted, hepatotropic, and lymphotropic RNA virus. More than 170 million people worldwide are chronically infected with HCV [1]. In high endemic areas such as Egypt and southern Italy local prevalence may reach 30% [2]. In Egypt genotype 4 constitutes 73.3% of all HCV positive cases [3]. HCV infection is the most common cause of chronic liver disease, accounts for 50% of all primary liver cancers [4].

HCV viremia has been known to provoke a plethora of autoimmune syndromes which has been referred to as extrahepatic manifestations (EHMs) which affect 40–70% of patients of chronic HCV infection mainly mixed cryoglobulinaemia (MCG) [5–7]. 50% to 80% of patients with essential MCG are infected with HCV and up to 50% of patients with hepatitis C infection have MCG [8]. In HCV/MCG patients, clinical involvement is mainly characterized by purpura, arthralgias, kidney disease, and peripheral neuropathy (PN) [9].

Neurological complications in HCV-infected patients occur predominantly in the peripheral nervous system (PNS). Their prevalence varies, and can be as high as 50% of cases and is primarily associated with MCG [10]. PNS involvement has also been reported in HCV-infected patients without MCG [11,12].

The pathophysiology of HCV related PN remains largely speculative; vascular deposition of HCV-RNA containing cryoglobulins (CGs), direct viral infection or perivascular mononuclear inflammatory cells may be at the origin of HCV associated inflammatory vascular lesions. However, it is likely that HCV neuropathy results from virus triggered immune mediated mechanisms rather than from direct nerve infection and in situ replication [13].

Recent evidence suggests that direct autoantibody reactions may play at least an additional role in affecting neuronal structures [14]. Within humoral autoimmunity to neuronal antigens, serum anti-ganglioside antibodies have been found in several central and peripheral neurological diseases and autoimmune disorders [15].

Gangliosides which are localized to the surface of central and peripheral neurones and exert a pivotal role in a variety of cell-surface mediated functions, include a wide array of molecules referred to as GM1, GM2, GD1a, GD1b, GT1b and GQ1b [16].

Many studies have reported various types of PN in western countries and Egypt [17–19,33]. The present study was undertaken to shed the light on prevalence and the characteristics of PN in a sample of Egyptian HCV patients and its possible correlations through clinical, laboratory and electrophysiological assessments.

2. Patients and methods

This study was carried out on 80 newly diagnosed, treatment-naïve HCV infection patients (48 males & 32 females) with mean age of 40.08 ± 7.29 years. Patients were selected from those being evaluated for antiviral therapy at the outpatient clinics of the Tropical Medicine department, Tanta University Hospitals, Egypt. In addition, twenty age and sex matched healthy volunteers were enrolled as control group.

2.1. Inclusion criteria

1. HCV-RNA positive patients by polymerase chain reaction (PCR).
2. The patients did not receive any treatment for HCV infection.

2.2. Exclusion criteria

- (a) Other diseases associated with neuropathy such as diabetes mellitus (abnormal HbA1c and fasting glucose test prior to enrollment), autoimmune disorder, renal failure, thyroid disorders, malignant hematological disorders, alcohol consumption (drinking low percentage alcohol beverages more frequently than once per week), HIV infection or drug addiction.
- (b) Impairment of the PNS other than neuropathy (e.g. tunnelopathies, radiculopathies, and nerve trauma).
- (c) Impairment of central sensory pathways (e.g. multiple sclerosis).

All patients gave an informed consent for a study. Patients were evaluated clinically, serologically, and electrophysiologically.

2.3. Clinical examination

Patients and control subjects were subjected to general examination with a special attention to hepatic & EHMs of HCV infection in patients. A diagnosis of clinical neuropathy was made when symptoms (weakness, sensory disturbances) and signs (weakness, atrophy, sensory abnormalities and/or reduced/absent tendon reflexes) of peripheral sensory and/or motor and cranial involvement were present. Self completed Leeds assessment of neuropathic symptoms and signs (S-LANSS) questionnaire was used as a diagnostic tool for neuropathic pain, on the scale, patients were asked how bad his pain

has been in the last week where: '0' means no pain and '10' means pain as severe as it could be [20].

2.4. Serological studies

Laboratory studies include, routine blood tests, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), IgM rheumatoid factor (RF), complement-4(C4) values, anti-nuclear antibody (ANA), detection and characterization of CGs according to Vermeersch et al. [21].

Anti-HCV antibodies were detected by third generation enzyme linked immunosorbent assay (ELIZA) (Roche Diagnostics, Mannheim, Germany) [22].

Quantitative HCV RNA test is based on the polymerase chain reaction (PCR) technique using a commercial kit (HEPA-Check-C, Nuclear Laser Medicine, Italy) and has a lower limit of detection of fewer than 100 copies of HCV RNA per ml of serum (50 IU/ml). It was classified into weak (100–100,000), moderate (100,000–1000,000) and high (> 1000,000) [23].

Anti-neuronal antibodies measurement: Anti-GM1 antibodies were measured by enzyme-linked immunoassay (ELISA). The microtiter plates were precoated with monosialo-ganglioside GM1. All the samples were diluted 50 times with a buffer saline solution and 100 µl diluted samples were pipetted into the wells (incubation buffer in blank). The plate was incubated for 2 h at 2–8 °C and after discarding the contents the wells were washed thrice with refrigerated wash buffer. Then 100 µl enzyme conjugated to horseradish peroxidase labeled antibody directed against IgG and IgM was added and incubated for 2 h at 2–8 °C. After washing the wells thrice with wash buffer, 100 µl of tetramethylbenzidine substrate (TMB) (allowed to come to ambient temperature prior to use) was added to each well. The plate was covered properly to protect from light and incubated for 30 min at room temperature on a plate mixture with 800–1000 rpm. The reaction was stopped by 100 µl of 0.25 M H₂ SO₄ and the absorbance was read at 450 nm. Antibody titers were calculated from optical densities (OD) as previously described by Pestronk [24]. Positivity cut-off titer was set at 1:400 for both IgM and IgG [25].

2.5. Abdominal ultrasonography

Abdominal ultrasonography was performed for patients only, where liver fibrosis was evaluated by ultrasound scoring system which ranges from 4 for a normal liver to 9 or more for advanced cirrhosis [26].

2.6. Liver biopsy

Liver specimens were obtained from patients for histopathological examination to confirm diagnosis, to exclude other causes, to determine the stage of fibrosis and grade of inflammation using modified Knodell score [27].

2.7. Electrophysiological techniques

The electrophysiological studies were performed in the electrophysiology unit, in the Rheumatology & Rehabilitation Department, Tanta University Hospitals, Egypt, using The Nihon Kohden Neuropack 2 (Nihon Kohden, Japan). Surface

temperature was maintained at 31–33 °C, the amplifier settings were at 10–2000 Hz. Nerve conduction studies were performed bilaterally according to a standardized protocol using surface electrodes as follows: motor conduction study of median, ulnar, posterior tibial and peroneal nerves, minimal F wave latencies of median, ulnar and posterior tibial nerves, soleus H reflex study and sensory conduction study using antidromic stimulation of median (digit II), ulnar (digit V), radial (The active electrode was placed over the tendon of the extensor pollicis longus muscle, stimuli were applied 10 cm proximal to the active electrode over the radius.) and sural nerves (lateral malleolus to 12 cm just lateral from the midline of the calf). Sural/radial nerve amplitude ratio (SRAR) was calculated by dividing the highest sural nerve amplitude by the highest superficial radial nerve amplitude.

Parameters were considered abnormal when they differed from the mean by ± 2.0 SD obtained from the control group. Patients were considered to have clinical neuropathy when they had one or more electrophysiological abnormalities in at least two nerves examined and it considered subclinical when they have electrophysiologic abnormalities with no clinical symptoms and signs of peripheral nerve involvement.

Statistical analysis: All data were analyzed using software (version 11, SPSS Inc., Chicago, Illinois). All data were presented as mean \pm standard deviation for the continuous variables, and as frequency and percentage for the discrete ones. Independent "t" test was used for when comparison between two groups was needed. Correlation between variables was examined using the Pearson's correlation coefficient. *P* value < 0.05 was considered statistically significant. Sensitivity was calculated for latency of H-reflex and SRAR.

3. Results

Eighty HCV patients were enrolled in this study, 48 males and 32 females, their ages ranged from 28 to 50 years. Control group, included 13 males and 7 females, their ages ranged from 28 to 48 years. All the patients were accidentally discovered and the cause of disease transmission was unknown, duration since discovery of HCV infection ranged from 3 to 30 months. ESR, CRP, RF, and ANA were significantly higher in patients than in controls ($p < 0.01$), while C4 was significantly lower in HCV patients ($p < 0.01$). Other laboratory parameters showed statistically significant difference between patients and controls including serum transaminases ($p < 0.001$) and anti-neuronal antibodies ($p < 0.001$). Detectable CGs (with a cryocrit greater than 0.1%) were found in 15% of patients. The main demographic, and laboratory features of patients and control group are shown in Table 1.

Quantitative PCR revealed that the majority of our patients (55%) had moderate viraemia, 30% had weak viraemia and 15% had high viraemia. Ultrasound scoring system of liver fibrosis showed that 87.5% of our patients had mild to moderate fibrosis, 12.5% had no fibrosis; while none of them had severe fibrosis.

The histological activity grading (HAI) demonstrated that 55% of the patients have minimal inflammation (score 1–4), while, 35% of them have mild inflammation (score 5–8) and 10% of them have moderate inflammation (score 9–12). On the other hand, staging of liver fibrosis (modified Knodell score) revealed that 50% of the patients had score 1 of fibrosis,

Table 1 Demographic and serological data of HCV patients and controls.

Parameters	HCV patients (<i>n</i> = 80)	Controls (<i>n</i> = 20)
Age	40.08 ± 7.29	37.00 ± 5.94
Sex (M/F)	48/32	13/7
Duration since disease discovery/months	14.60 ± 10.29	–
ESR (mm/h)	19.82 ± 7.89*	12.53 ± 6.88
CRP (mg/dl)	6.30 ± 4.4*	4.400 ± 0.73
RF (mg/dl)	121 ± 80*	7.20 ± 1.52
ANA (U/ml)	12.51 ± 2.8*	5.32 ± 1.7
C4 (mg/dl)	13.85 ± 6.5*	21.49 ± 9.7
ALT (U/l)	51.3 ± 40.2**	23.8 ± 8.69
AST (U/l)	54.1 ± 40.3**	20.07 ± 6.5
CG + ve patients (<i>n</i> & %)	12 (15%)	–
IgM anti-GM1 titer	1:570 ± 1:400**	1:170 ± 1:167
IgG anti-GM1 titer	1:537 ± 1:409**	1:200 ± 1:100

HCV: Hepatitis C virus; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; ALT: alanine aminotransferase; AST: aspartate aminotransferase; RF: rheumatoid factor; C4: complement-4; ANA: anti-nuclear antibody; CG: cryoglobulin; anti-GM1: anti-ganglioside antibodies.

* <0.01 compared to controls.

** <0.001 compared to controls.

30% of them had score 2 of fibrosis, 10% of them had score 3 of fibrosis, 5% of them had score 4 of fibrosis and 5% of them have incomplete cirrhosis (score 5).

Neurological examinations are showed in Table 2. Clinical PN was diagnosed in 36 out of 80 patients (45%). All of them had electrophysiological evidence of PN. Moreover, electrophysiological examination disclosed a subclinical PN in 18 additional patients (22.5%). Totally, 54 of our patients (67.5%) were diagnosed to have neuropathy by electrophysiological examination.

Electrophysiological studies showed axonal neuropathy in 38 patients out of the 54 neuropathy patients (70.3%) which was mainly sensory affecting lower limbs (Table 3). Meanwhile, 29.7% of them showed mixed axonal and demyelinating sensorimotor polyneuropathy; sensory and motor nerves in the lower limbs were involved predominantly and sensory nerves were more affected than motor nerves. In the lower limbs, MCVs were reduced in 14 patients, reduction of CMAP amplitude in 40 patients, abnormal F wave latency in 20 patients and abnormal H-reflex in 40 patients. In the upper limbs

MCVs were reduced in 6 patients, reduction of amplitude in 14 patients and abnormal F wave latency in 16 patients. SNPs of sural nerve were absent in 5 patients, abnormal amplitude and velocities in 30 patients and abnormal SRSR amplitude in 40 patients. In the upper limbs SCVs reduced in 8 patients.

Sensitivity of H reflex and SRAR in HCV patients is the same (55.5%) but combination of both tests increased sensitivity to 94.4%.

There was significant correlation between most of nerve conduction parameters with age of the patients, disease duration, ESR, CRP, RF, and IgM & IgG anti-GM1, load of viraemia and CG ($p < 0.001$). All of our CG+ patients had PN (10 clinical, 2 subclinical). Moreover, there was significant negative correlation between nerve conduction parameters with level of C4. Nevertheless, there was no significant correlation between nerve conduction parameters with staging of liver fibrosis either by ultrasound scoring system or modified Knodells score.

Abnormal titers of anti-neuronal antibodies were found to be associated with electrophysiological abnormalities in 50 out of the 54 neuropathy cases.

Table 2 Clinical neurological data in HCV patients.

Neurological manifestations	Hepatitis C patients (<i>n</i> = 80)	
No neurological deficit	<i>N</i>	44
(symptoms or signs)	%	55
Sensory manifestation	<i>N</i>	34
	%	42.5
Motor manifestation	<i>N</i>	0
	%	0
Sensory-motor manifestation	<i>N</i>	2
	%	2.5
Cranial nerve affection	<i>N</i>	0
	%	0
S-LANSS score	<i>N</i>	35
	%	43.7%

All data were presented as frequency and percentage. HCV: Hepatitis C virus; S-LANSS: Leeds assessment of neuropathic symptoms and signs.

4. Discussion

The population of Egypt has a heavy burden of liver disease, mostly due to chronic HCV infection. The overall prevalence of antibody to HCV in the general population is around 15–20% [28]. The majority of the literature reporting on the neurological manifestations of HCV patients points to the PNS and describes painful neuropathies [29]. Antibodies against several neural antigens have been associated with a number of chronic immune-mediated neuropathies [30]. Detection of these anti-neuronal antibodies might provide additional prognostic insights and suggest a new scenario of the pathogenesis of the neurological manifestations of HCV related MCG [14].

In the current study, 70% of our patients were over 40 years which agrees with Frank et al. [28] who reported increased prevalence of HCV with age, and they explained it by the possibility of exposure of these groups to schistosomiasis

Table 3 Motor and sensory nerve conduction studies in HCV patients and controls.

Electrophysiological parameters	Hepatitis C patients	Controls (<i>n</i> = 20)
<i>Median motor nerve (n = 80)</i>		
MCV (m/s)	55.43 ± 6.0	58.29 ± 8.3
DL (ms)	3.95 ± 0.45	3.78 ± 0.29
Amp (mV)	4.24 ± 2.28*	6.88 ± 2.77
F wave (ms)	26.5 ± 4.87	26.83 ± 1.6
<i>Ulnar motor nerve (n = 80)</i>		
MCV (m/s)	57.1 ± 7.49	56.4 ± 5.95
DL (ms)	2.93 ± 0.51	2.79 ± 0.48
Amp (mV)	4.21 ± 2.91*	7.26 ± 1.60
F wave (ms)	25.66 ± 6.59	26.77 ± 2.6
<i>Peroneal nerve (n = 80)</i>		
MCV (m/s)	46.0 ± 6.25*	51.67 ± 4.3
DL (ms)	3.97 ± 0.83*	3.3 ± 0.144
Amp (mV)	2.87 ± 1.88*	6.55 ± 1.18
<i>Posterior tibial nerve (n = 80)</i>		
MCV (m/s)	44.1 ± 5.1*	48.9 ± 2.83
DL (ms)	4.66 ± 1.12*	3.17 ± 0.78
Amp (mV)	5.21 ± 3.33*	8.11 ± 3.01
F wave (ms)	48.65 ± 9.68*	45.28 ± 2.7
H-reflex (ms)	31.2 ± 5.96*	29.11 ± 0.9
<i>Median sensory nerve (n = 80)</i>		
W-F SCV (m/s)	50.69 ± 5.38	52.36 ± 7.06
SAP ampl. (mcV)	21.3 ± 10.4	26.1 ± 15.6
<i>Ulnar sensory nerve (n = 80)</i>		
W-F SCV (m/s)	58.73 ± 5.43	57.52 ± 8.19
SAP ampl. (mcV)	12.82 ± 9.96*	23.6 ± 10.9
<i>Radial sensory nerve (n = 80)</i>		
W-F SCV (m/s)	54.27 ± 8.43	57.02 ± 3.88
SAP ampl. (mcV)	21.4 ± 10.7	22.99 ± 4.16
<i>Sural nerve (n = 75)</i>		
SCV (m/s)	44.4 ± 11.8*	51.38 ± 5.09
SAP ampl. (mcV)	6.26 ± 4.43*	14.77 ± 3.14
S/R amplitude ratio	0.31 ± 0.21*	0.640 ± 0.13

MCV: motor conduction velocity; SCV: sensory conduction velocity, DL = distal latency; Amp: amplitude of compound motor action potential or sensory action; SRAR: Sural/Radial nerve amplitude ratio.

* Statistically significant <0.001 compared to controls.

campaigns in Egypt, and the use of contaminated needles or syringes during campaigns.

The majority of our patients was males (60%). Habib et al. [31], revealed that the HCV is more prevalent in males than females in Egypt due to the existence of two common potential HCV exposures for males: (1) shaving by a community barber using the same razor blade and (2) smoking tobacco with a water pipe (Shisha) which can theoretically result in exposure to blood from individuals with gingivitis.

PN was clinically diagnosed in 45% out of our patients, 42.5% showed sensory PN. The predominance of sensory PN among our patients agrees with Sterling and Bralow [32], who demonstrated that sensory deficiencies are more common than motor loss, and that sensory symptoms may persist for months to years before any motor deficit become clinically evident. On the other hand, the high prevalence of clinical PN among our patients is close to that reported by Cacoub et al. [10], which was up to 50%. Meanwhile, it was not consistent with previous Egyptian studies. The highest prevalence of PN among Egyptian HCV patients was 30% reported by Abul

Hassan et al. [33], followed by 15.63% in the study of El Ghoneimy et al. [19] and 10% in the study of Abo Al-Soud et al. [34]. In western countries, Gomes et al. [35] reported PN prevalence of 34.6%, while other studies reported prevalence up to 10.6% [7,13,36].

This wide variability of PN prevalence among different studies can be attributed to the model of patient enrollment, which in our study was based on the presence of HCV infection in untreated patients, independently of the signs or symptoms. It also can be attributed to the use of different methods for PN clinical evaluation.

It was mentioned that pure clinical assessment tends to underestimate PNS involvement in the HCV population [13] and that symptoms alone have relatively poor diagnostic accuracy in predicting the presence of PN and stressed on the importance of electrodiagnosis for its diagnosis [37]. We confirmed this statement when electrophysiological examination of our patients disclosed a subclinical PN in 18 additional patients (22.5%). This is in keeping with some authors who diagnosed subclinical PN in their patients [13,34], and

disagrees with Ripault et al. [36] who reported equal prevalence of clinical and electrophysiological PN, and with Gomes et al. [35] who found clinical PN to be more than electrophysiological PN.

In the current study, a total of 67.5% (54/80) of our patients were diagnosed to have PN by electrophysiological examination. This finding disagrees with many authors where their percentage ranged from 8% to 37% [13,34–36,38,39].

Out of the 54 neuropathy patients, 38 patients (70.3%) showed axonal neuropathy which was mainly sensory affecting lower limbs more than upper limbs. While 16 patients (29.7%), showed mixed axonal and demyelinating sensorimotor polyneuropathy; with the same distribution and predominance of sensory affection. This finding is in accordance with some authors who demonstrated axonal type of neuropathy among their HCV patients with distal sensory or sensory-motor affection [7,33] or multifocal mononeuropathy. The underlying pathogenetic mechanisms for this complication are systemic CG and vasculitis [11,12,34,36,40–44]. Peripheral demyelinating neuropathy has been rarely described, most often in CG+ve patients and results from the heterogeneity of the pathophysiological mechanisms of neuropathies [11,42,45–47].

It has been hypothesized that SRAR can be used for the detection of early axonal loss; because the sural SNAP amplitude will decrease first, thereby also decreasing the SRAR value [48]. Our study showed that sensitivity of H-reflex and SRAR HCV patients was the same (55.5%) but combination of both tests increased sensitivity to 94.4%. This agrees with the study by Kim et al. [49] Moreover, Rutkove et al. [50] reported that an SRAR of less than 0.40 was a strong predictor of axonal polyneuropathy, with 90% sensitivity and 90% specificity, as compared to absolute sural amplitude which had sensitivity of only 66%.

The big variation of PN prevalence in HCV patients among different studies may be due to the fact that, it is a multifactorial disease process. Ripault et al. [36] suggested that the most important factor is the viral factors such as, viral genotypes as there is wide difference between the viral genotypes in Egypt and western countries.

15% of our patients showed positive CGs, which is very close to the findings of Gad et al. [51], who reported CGs prevalence of 14% among HCV genotype 4 Egyptian patients. While, this finding disagrees with many authors who reported CG prevalence ranging from 19% up to 54% among their HCV patients [7,52–55], and with Persico et al. [56] and Verbaan et al. [57], who demonstrated 0.8% and 0% prevalences of CG in their patients consecutively.

The low prevalence of CGs among our HCV population can be attributed to: (a) HCV genotype 4 which is the common type among Egyptian patients is associated with low prevalence of CG compared to high prevalence in Japanese patients infected with genotype 1b [51], and to HCV genotype 2a infected patients. (b) The relatively short disease duration, as Lunel et al. [52] showed that the duration of the disease in HCV patients with MCG was almost twice as long than in patients without MCG and (c) relatively younger age of our patients, which agrees with some studies where it was noted that patients with MCG were of older age while sex was not a risk factor [58,59].

All of our CG+ patients had PN (10 clinical, 2 subclinical). None of them showed clinical manifestations of MCG. This agrees with the authors stating that HCV related PN is usually

associated with CG [10,11,19,36,39] and that the presence of serum CGs is predictive of more severe and widespread neuropathic involvement [12,60] and also with those who clarified that the only 13–30% of patients with CG are symptomatic [61].

Our patients showed significantly higher levels of anti-neuronal antibodies which were associated with electrophysiological abnormalities in 50 out of the 54 neuropathic patients. This finding is in keeping with Alpa et al. [62] who reported high plasma IgM and IgG anti-GM1 titers in MCG patients, and 61% of patients having abnormal titers were associated with clinical or subclinical evidence of neuropathy. Moreover, Ortiz et al. [63] concluded that high IgM anti ganglioside titers are involved in the etiopathogenesis of demyelinating neuropathies.

Statistical analysis showed a strong correlation between the presence of PN and age of patients, disease duration, load of viraemia, ESR, CRP, RF, IgM & IgG anti-GM1 and the presence of CGs. In addition; there was significant negative correlation between PN and C4 levels. On the other hand, no significant correlation could be found between PN and ANA, staging of liver fibrosis either by ultrasound scoring system or modified Knodells score.

These results are in keeping with Zaltron et al. [39] who reported a strong correlation between old age and PN although it was unrelated to cryocrit levels or type of CG, and with higher RF and reduced C4 activity, and with Santoro et al. [13] who demonstrated that electrophysiological evidence of PN was significantly associated with older age and virus load, but not with disease duration or CG. Also with Nemni et al. [12] who found that HCV-related neuropathy was significantly associated with diminished serum C4 levels. Nevertheless, Lidove et al. [60], reported that RF was always negative and C4 complement level was always normal among their HCV patients.

The significant relation between PN and virus load supports the mechanism which denotes that HCV may have a direct role in the pathogenesis of neuropathy. Furthermore, it support the immune hypothesis for the pathogenesis of PN as evidenced by the correlation between electrophysiological study and RF & diminished C4, which is in accordance with Sterling and Bralow [32], who found that RF is often positive in chronic HCV.

In conclusion, our findings demonstrate that PN exists in high prevalence among Egyptian HCV patients, and is commonly associated with CG. It is mainly of axonal sensory type with more affection of lower limbs. PN was found to correlate with the age of the patients, disease duration, ESR, CRP, RF, HCV viraemia, IgM and IgG anti-GM1 and hypocomplementinemia. It is recommended that HCV patients should be investigated for the presence of CGs even in the absence of clinical manifestations suggestive of MCG. HCV patients with no clinical evidence of neuropathy should be evaluated by electrodiagnosis, especially if they are CG+ve.

Conflict of interest

The authors have no conflict of interest.

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